CONFIDENTIAL

THE COUNCIL FOR TOBACCO RESEARCH - U. S. A.

February 18, 1966

MEMORANDUM

TO: The committee comprising Dr. Cattell, Chm., Dr. Bing and Dr. Jacobson.

FROM: Robert C. Hockett

SUBJECT: Site visit to Dr. Hyman Engelberg of Cedars-Sinai Medical Center, Los Angeles, California. No. 513.

On February 6, I visited Dr. Hyman Engelberg in his Los Angeles laboratory to discuss further the application (#513). This was discussed at the December meeting of the Board (and should be in your files), but action was deferred and a site visit prescribed. It was hoped that Dr. Bing could pay the visit but this turned out to be impossible to arrange before the March 5-6 Board meeting. However he kindly furnished me the following comment from a colleague in the field of hematology:

> "This is an interesting protocol. I am, however, wondering as to why the investigator is not planning to perform other coagulation tests in order to clarify the possible factor affecting the thrombus formation time. A complete coagulation studies to include recalcification time, partial thromboplastin time, prothrombin time, thrombin time, Factor V, fibrinogen, antithrombin, euglobulin lysis time, profibrinolysin, antifibrinolysin and platelet counts may throw further light on this problem. It seems to me that in conjunction with the proposed tests, a complete coagulation profile may be very useful. I am not aware of any report describing the effect of smoking on various coagulation tests. His approach otherwise looks very reasonable and worthwhile".

This comment was shown to Dr. Engelberg without revealing its origin. His reply was that all these things obviously ought to be done sooner or later. He does not want to add them to his program at the present moment because he does not have a skilled technician for such measurements available at the moment. He would rather spend his own time for the present on various extensions of this particular measurement that he has developed. The features that recommend it to him are its speed, simplicity and reproducibility. He feels that many of the other tests are tricky and poorly reproducibile, several having their own advocates with resultant controversy and confusion. He says he would gladly cooperate with any hematologist whom we might wish to designate and would not only furnish duplicates of his instrument (it is relatively inexpensive) but train technicians in its use. He would be glad to have cooperation on study of the relations between these tests and his own. He believes that the early change he observes is antecedent to the coagulation process.

He showed me his instrument, of which he has several duplicates, and I was impressed by the evidence of the replicability of results. Timing is essential and the whole test must be carried out immediately, with timing, after drawing the blood sample. Hence the need for several instruments.

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MEMORANDUM - Cont'd.

Both epinephrine and nor-epinephrine produce a shortening of the "thrombus formation time" (see attached charts). Changes in free fatty acids in the serum seem to bear a kind of reciprocal relation to the "time of thrombus formation", but these changes are prevented by previous administration of a big dose of nicotinic acid. Hence he thinks that free fatty acids are not mediators of the effect.

I gave him some nicotine bitartrate in ampoules several weeks ago and he has made a few observations on the effects of intravenously administered nicotine on the "thrombus formation speed". As shown on another chart the effect of nicotine is similar to the effect of epinephrine or nor-epinephrine. This suggests that the nicotine effect might be mediated through the catecholamines. This will be studied by use of agents that should block action of the latter to see whether the nicotine effect persists or not.

Engelberg is also comparing the effects of catecholamines and nicotine administered to the subject before drawing blood and added to the blood after drawing. Effects are not identical, which suggests that they are mediated through some chain of events in the body rather than the result of direct action.

He has already shown that adenosine diphosphate has a direct effect on this measurement when added in vitro and that there are variations in the levels of this agent in freshly drawn blood. Also adenosine diphosphate tends to increase with time in drawn blood in vitro.

On the whole Dr. Engelberg pretty well convinced me that he has enough to do to keep quite busy for awhile without undertaking a lot of "conventional" hematological tests in parallel.

This does leave the problem of "bridging" between this test and other kinds of observations in order to get some idea of the clinical meaning of a "shortened thrombus formation time".

Because of its speed, simplicity and replicability the test could be included in prospective studies of large populations, such as the Framingham study. I raised this suggestion and Engelberg liked it. The Framingham group includes individuals who have developed clinical cardiovascular disease and many others who have not. A large body of data has been collected and recorded on all and is being kept up to date by re-examinations. We now have a finger in the project through Damon, Seltzer and McNiven and could perhaps interest them in including this test in their data collection. If so, Engelberg is ready to cooperate. Of course, we could encounter an impasse, since they might want evidence of the significance of the test before undertaking to include it!

Engelberg is, of course, a clinically oriented man in private practise. He impressed me, however, as being alert, energetic, a clear thinker and rather well-read. It might be well worth while to give him his head for a year and see what results. The study has a possibility of direct bearing on our main targets. If the Framingham idea could be worked out and/or cooperation of a hematologist arranged for an integrated study, the values should be enhanced.

R.C.H.

Personal Opinion:

The Engelberg proposal will be placed on the agenda for March 5-6 as a deferred application.

P.S. : A manuscript just received from Dr. Engelberg is enclosed: The Effect of Catecholamines Upon the In Vitro Thrombosis of Human Blood. Engelberg and Futterman.

R.C.H.

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